2 Compliance Program Guidance Manual for FDA Staff: Drug Manufacturing Inspections

I. BACKGROUND

A primary mission of the Food and Drug Administration (FDA) is to conduct comprehensive regulatory coverage of all aspects of production and distribution of drugs and drug products to assure that such products meet the 501(a)(2)(B) requirements of the Food, Drugs and Cosmetics Act. The FDA has developed two basic strategies:

1. Evaluating through factory inspections, including the collection and analysis of associated samples, the conditions and practices under which drugs and drug products are manufactured, packed, tested, and held
2. Monitoring the quality of drugs and drug products through surveillance activities such as sampling and analyzing products in distribution

This compliance program is designed to provide guidance for implementing the first strategy. Products from production and distribution facilities covered under this program are consistently of acceptable quality if the firm is operating in a state of control. The Drug Product Surveillance Program (CP 7356.008) provides guidance for the latter strategy.

II. IMPLEMENTATION

A. Objectives

The goal of this program's activities is to minimize consumers exposure to adulterated drug products. Under this program, inspections and investigations, sample collections and analyses, and regulatory or administrative follow-up are made:

- To determine whether inspected firms are operating in compliance with applicable current Good Manufacturing Practices (CGMPs) requirements and, if not, to provide the evidence for actions to prevent adulterated products from entering the market; and, as appropriate, to remove adulterated products from the market and to take action against persons responsible as appropriate
- To provide CGMP assessment, which may be used in efficient determination of acceptability of the firm in the preapproval review of a facility for new drug applications
- To provide input to firms during inspections to improve their compliance with regulations
- To continue the FDA's unique expertise in drug manufacturing in determining the adequacy of CGMP requirements, FDA CGMP regulatory policy, and guidance documents.

B. Strategy

1. Biennial Inspection of Manufacturing Sites

Drugs and drug products are manufactured using many physical operations to bring together components, containers, and closures into a product that is released for distribution. Activities found in drug firms can be organized into systems that are sets of operations and related activities. Control of all systems helps to ensure that the firm will produce drugs that are safe, have the identity and strength, and meet the quality and purity characteristics as intended.

Biennial inspections (every 2 years) of manufacturing sites, which include repackaging, contract labs, etc., help to:

- Reduce the risk that adulterated products are reaching the marketplace
- Increase communication between the industry and the Agency
- Provide for timely evaluation of new manufacturing operations in the firm
- Provide for regular feedback from the Agency to individual firms on the continuing status of the firm's GMP compliance

This program applies to all drug manufacturing operations.

Currently, not enough FDA resources are available to audit every aspect of CGMP in every manufacturing facility during every inspection visit. Profile classes generalize inspection coverage from a small number of specific products to all the products in that class. This program

establishes a systems approach to further generalize inspection coverage from a small number of profile classes to an overall evaluation of the firm. Reporting coverage for every profile class as defined in Field Accomplishment and Compliance Tracking System (FACTS), in each biennial inspection, provides the most broadly resource-efficient approach. Biennial updating of all profile classes will allow for CGMP acceptability determinations to be made without delays resulting from revisiting the firm. This will speed the review process, in response to compressed timeframes for application decisions and in response to provisions of the FDA Modernization Act of 1997 (FDAMA). This will allow for Preapproval Inspections/Investigations Program inspections and Postapproval Audit Inspections to focus on the specific issues related to a given application or the firm's ability to keep applications current.

The inspection is defined as audit coverage of two or more systems, with mandatory coverage of the Quality System (see the system definitions in Section II.B.3.). Inspection options include different numbers of systems to be covered depending on the purpose of the inspection. Inspecting the minimum number of systems, or more systems as deemed necessary by the regional District of the FDA, will provide the basis for an overall CGMP decision.

2. Inspection of Systems

Inspections of drug manufacturers should be made and reported using the system definitions and organization in this compliance program. Focusing on systems instead of on profile classes will increase efficiency in conducting inspections because the systems are often applicable to multiple profile classes. One biennial inspection visit will result in a determination of acceptability/nonacceptability for all profile classes. Inspection coverage should be representative of all the profile classes manufactured by the firm. The efficiency will be realized because multiple visits to a firm will not be needed to cover all profile classes; delays in approval decisions will be avoided because up-to-date profile class information will be available at all times.

Coverage of a system should be sufficiently detailed, with specific examples selected, so that the system inspection outcome reflects the state of control in that system for every profile class. If a particular system is adequate, it should be adequate for all profile classes manufactured by the firm. For example, the way a firm handles “materials” (i.e., receipt, sampling, testing, acceptance, etc.) should be the same for all profile classes. The investigator should not have to inspect the Material System for each profile class. Likewise, the Production System includes general requirements such as standard operating procedure (SOP) use, charge-in of components, equipment identification, and in-process sampling and testing, which can be evaluated through selection of example products in various profile classes. Under each system, there may be something unique for a particular profile class (e.g., under the Materials System, the production of Water for Injection USP (*U.S. Pharmacopeia*) for use in manufacturing. Selecting unique functions within a system will be at the discretion of the lead investigator). Any given inspection need not cover every system (see Section III).

Complete inspection of one system may necessitate further followup of some items within the activities of another/other system(s) to fully document the findings. However, this coverage does not constitute nor require complete coverage of these other systems.

3. A Scheme of Systems for the Manufacture of Drugs and Drug Products

A general scheme of systems for auditing the manufacture of drugs and drug products consists of the following:

1. *Quality System* — This system assures overall compliance with CGMPs and internal procedures and specifications. The system includes the quality control unit and all its review and approval duties (e.g., change control, reprocessing, batch release, annual record review, validation protocols, and reports). It includes all product defect evaluations and evaluation of returned and salvaged drug products. (See the CGMP regulation, 21 CFR 211 Subparts B, E, F, G, I, J, and K.)
2. *Facilities and Equipment System* — This system includes the measures and activities that provide an appropriate physical environment and the resources used in the production of the drugs or drug products. It includes:
   a. Buildings and facilities along with maintenance
   b. Equipment qualifications (installation and operation); equipment calibration and preventative maintenance; and cleaning and validation of cleaning processes as appropriate; process performance qualification will be evaluated as part of the inspection of the overall process validation that is done within the system where the process is employed
   c. Utilities not intended for incorporation into the product such as heating, ventilating, and air conditioning (HVAC), compressed gases, steam, and water systems. (See the CGMP regulation, 21 CFR 211 Subparts B, C, D, and J.)
3. *Materials System* — This system includes measures and activities to control finished products, components, including water or gases that are incorporated into the product, containers, and closures. It includes validation of computerized inventory control processes, drug storage,

distribution controls, and records. (See the CGMP regulation, 21 CFR 211 Subparts B, E, H, and J.)

4. *Production System* — This system includes measures and activities to control the manufacture of drugs and drug products including batch compounding, dosage form production, in-process sampling and testing, and process validation. It also includes establishing, following, and documenting performance of approved manufacturing procedures. (See the CGMP regulation, 21 CFR 211 Subparts B, F, and J.)
5. *Packaging and Labeling System* — This system includes measures and activities that control the packaging and labeling of drugs and drug products. It includes written procedures, label examination and usage, label storage and issuance, packaging and labeling operations controls, and validation of these operations. (See the CGMP regulation, 21 CFR 211 Subparts B, G, and J.)
6. *Laboratory Control System* — This system includes measures and activities related to laboratory procedures, testing, analytical methods development and validation or verification, and the stability program. (See the CGMP regulation, 21 CFR 211 Subparts B, I, J, and K.)

The overall theme in devising this scheme of systems was the subchapter structure of the CGMP regulation. Every effort was made to group whole subchapters together in a rational set of six systems that incorporates the general scheme of pharmaceutical manufacturing operations.

The organization and personnel, including appropriate qualifications and training, employed in any given system, is evaluated as part of that system's operation. Production, control, or distribution records required to be maintained by the CGMP regulation and selected for review should be included for inspection audit within the context of each of the previously described systems. Inspections of contract companies should be within the systems for which the products or services are contracted as well as their quality systems.

As this program approach is implemented, the experience gained will be reviewed to make modifications to the system definitions and organization as needed.

III. PROGRAM MANAGEMENT INSTRUCTIONS

A. Definitions

1. Surveillance Inspections

a. The Full Inspection Option

The Full Inspection Option is a surveillance or compliance inspection that is meant to provide a broad and deep evaluation of the firm's CGMP. This is done when little or no information is known about a firm's CGMP compliance (e.g., for new firms); or for firms where doubt exists about the CGMP compliance in the firm (e.g., a firm with a history of documented short-lived compliance and recidivism); or follow-up to previous regulatory actions. Based on findings of objectionable conditions (as listed in Section V) in one or more systems — a minimum of two systems must be completed — a Full Inspection may revert to the Abbreviated Inspection Option, with District concurrence (see Section III.B.1.). During the course of a Full Inspection, verification of Quality System activities may require limited coverage in other systems. The Full Inspection Option normally includes an inspection audit of at least four of the systems, one of which must be the Quality System (the system that includes the responsibility for the annual product reviews).

b. The Abbreviated Inspection Option

The Abbreviated Inspection Option is a surveillance or compliance inspection that is meant to provide an efficient update evaluation of a firm's CGMP. The abbreviated inspection provides documentation for continuing a firm in a satisfactory CGMP compliance status. Generally, this is done when a firm has a record of satisfactory CGMP compliance, with no significant recall or product defect or alert incidents, or with little shift in the manufacturing profiles of the firm within the previous 2 years (see Section III.B.2.). A full inspection may revert to an abbreviated inspection based on findings of objectionable conditions as listed in Section V in one or more systems. The Abbreviated Inspection Option normally includes an inspection audit of at least two of the systems, one of which must be the Quality System (the system which includes the responsibility for the annual product reviews). The District drug program managers should ensure that the optional systems are rotated in successive abbreviated inspections. During the course of an abbreviated inspection, verification of quality system activities may require limited coverage in other systems. Some firms participate in a limited part of the production of a drug or drug product (e.g., a contract laboratory). Such firms may employ only two of the systems defined. In these cases, the inspection of the two systems comprises inspection of the entire firm; this is considered as the Full Inspection Option.

c. Selecting Systems for Coverage

The selection of the system(s) for coverage will be made by the FDA's Regional District Office based on such factors as a given firm's specific operation, history of previous coverage, history of compliance, or other priorities determined by the District Office.

2. Compliance Inspections

Compliance inspections are inspections conducted to evaluate or verify compliance corrective actions after a regulatory action has been taken. First, the coverage given in compliance inspections must be related to the deficient areas and subjected to corrective actions.

In addition, coverage must be given to systems because a determination must be made on the overall compliance status of the firm after the corrective actions are taken. The firm is expected to address all its operations in its corrective action plan after a previously violative inspection, not just the deficiencies noted in the FDA-483 (inspectional observations). The Full Inspection Option should be used for a compliance inspection, especially if the Abbreviated Inspection Option was used during the violative inspection.

Compliance Inspections include "For Cause Inspections." For Cause Inspections are compliance inspections that are conducted to investigate a specific problem that has come to the attention of some level of the agency. The problems may be indicated in Field Alert Reports (FARs), industry complaints, recalls, indicators of defective products, etc. Coverage of these areas may be assigned under other compliance programs; however, expansion of the coverage to a GMP inspection must be reported under this program. For Cause Inspections may be assigned under this program as the need arises.

3. State of Control

A drug firm is considered to be operating in a "state of control" when it employs conditions and practices that assure compliance with the intent of Sections 501(a)(2)(B) of the Act and portions of the CGMP regulations that pertain to their systems. A firm in a state of control produces finished drug products for which there is an adequate level of assurance of quality, strength, identity, and purity.

A firm is "out of control" if any one system is out of control. A system is out of control if the quality, identity, strength, and purity of the products resulting from that(those) system(s) cannot be adequately assured. Documented CGMP deficiencies provide the evidence for concluding that a system is not operating in a state of control. See Section V, "Regulatory/Administrative Strategy," for a discussion of compliance actions based on inspection findings demonstrating out of control systems/firm.

4. Drug Process

A drug process is a related series of operations that result in the preparation of a drug or drug product. Major operations or steps in a drug process may include mixing, granulation, encapsulation, tabletting, chemical synthesis, fermentation, aseptic filling, sterilization, packing, labeling, and testing.

5. Drug Manufacturing Inspection

A Drug Manufacturing Inspection is a factory inspection in which evaluation of two or more systems, including the Quality System, is done to determine if manufacturing is occurring in a state of control.

B. Inspection Planning

The Field will conduct drug-manufacturing inspections and maintain profiles or other monitoring systems, which ensures that each drug firm receives biennial inspectional coverage, as provided for in the strategy.

The District Office is responsible for determining the depth of coverage given to each drug firm. CGMP inspectional coverage shall be sufficient to assess the state of compliance for each firm.

The frequency and depth of inspection should be determined by the statutory obligation, the firm's compliance history, the technology employed, and the characteristics of the products. When a system is inspected, the inspection of that system may be considered applicable to all products that use it. Investigators should select an adequate number and type of products to accomplish coverage of the system. Selection of products should be made so that coverage is representative of the firm's overall abilities to manufacture within CGMP requirements.

Review of new drug application/anticipated new drug application (NDA/ANDA) files may assist in selecting significant drug processes for coverage in the various systems. Significant drug processes are those that utilize all the systems in the firm very broadly and contain steps with unique or difficult manipulation in the performance of a step. Products posing special manufacturing features (e.g., low-dose products, narrow therapeutic range drugs, combination drugs, modified release products, etc.) and new products made under an approved drug application should be considered first in selecting products for coverage.

The health significance of certain CGMP deviations may be lower when the drug product involved has no major systemic effect or no dosage limitations, such as in products like calamine lotion or over-the-counter (OTC) medicated shampoos. Such products should be given inspection coverage with appropriate priority.

Inspections for this compliance program may be performed during visits to a firm when operations are being performed for other compliance programs or other investigations.

C. Profiles

The inspection findings will be used as the basis for updating all profile classes in the profile screen of the FACTS EIR coversheet that is used to record profile/class determinations. Normally, an inspection under this

systems approach will result in the update of all profile classes.

IV. INSPECTIONAL OBSERVATIONS

A. Investigational Operations

1. General

Review and use the CGMPs for Finished Pharmaceuticals (21 CFR 210 and 211) to evaluate manufacturing processes. Use the Guides to Inspection published by the Office of Regional Operations for information on technical applications in various manufacturing systems.

The investigator should conduct inspections according to the "Strategy" section in Part II of this compliance program. Recognizing that drug firms vary greatly in size and scope, and manufacturing systems are more or less sophisticated, the approach to inspecting each firm should be carefully planned. For example, it may be more appropriate to review the Quality System thoroughly before entering production areas in some firms; in others, the Quality System review should take place concurrently with inspection of another system or systems selected for coverage. The complexity and variability necessitate a flexible inspection approach — one that not only allows the investigator to choose the inspection focus and depth appropriate for a specific firm, but also directs the performance and reporting on the inspection within a framework that will provide for a uniform level of CGMP assessment. Furthermore, this inspection approach provides for fast communication and evaluation of findings.

Inspectional Observations noting CGMP deficiencies should be related to a requirement. Requirements for the manufacture of drug products (dosage forms) are in the CGMP regulation and are amplified by policy in the Compliance Policy Guides, or case precedents. CGMP requirements apply to the manufacture of distributed prescription drug products, OTC drug products, approved products, and products not requiring approval, as well as drug products used in clinical trials. The CGMP regulations are not direct requirements for manufacture of active pharmaceutical ingredients (APIs); the regulations should not be referenced as the basis for a GMP deficiency in the manufacture of APIs, but they are guidance for CGMP in API manufacture.

Guidance documents do not establish requirements; they state examples of ways to meet requirements. Guidance documents are not to be referred to as the justification for an inspectional observation. The justification comes from the CGMPs. Current Guides to Inspection and Guidance to Industry documents provide interpretations of requirements, which may assist in the evaluation of the adequacy of CGMP systems.

Current inspectional observation policy as stated in the inspection operations manual (IOM) says that the FDA-483, when issued, should be specific and contain only significant items. For this program, inspection observations should be organized under separate captions by the systems defined in this program. List observations in order of importance within each system. Where repeated or similar observations are made, they should be consolidated under a unified observation. For those Districts utilizing Turbo EIR, a limited number of observations can be common to more than one system (e.g., organization and personnel including appropriate qualifications and training). In these instances, put the observation in the first system reported on the FDA-483 and in the text of the EIR, reference the applicability to other systems where appropriate. This should be done to accommodate the structure of Turbo EIR, which allows individual citation once per FDA-483. Refrain from using unsubstantiated conclusions. Do not use the term "inadequate" without explaining why and how. Refer to the policy in the IOM, Chapter 5, Section 512 and Field Management Directive 120 for further guidance on the content of Inspectional Observations.

Specific specialized inspectional guidance may be provided as attachments to this program, or in requests for inspection, assignments, etc.

2. Inspection Approaches

This program provides two surveillance inspectional options: Abbreviated Inspection Option and Full Inspection Option (see the definitions of the inspection options in Part II of this compliance program).

1. *Selecting the Full Inspection Option* — The Full Inspection Option will include inspection of at least four of the systems as listed in Part II "Strategy," one of which must be the Quality System.
   a. Select the Full Inspection Option for an initial FDA inspection of a facility. A full inspection may revert to the Abbreviated Inspection Option, *with District concurrence,* based on the finding of objectionable conditions as listed in Part V in one or more systems (a minimum of two systems must be completed).
   b. Select the Full Inspection Option when the firm has a history of fluctuating into and out of compliance. To determine if the firm meets this criterion, the District should utilize all information at its disposal, such as, inspection results, results of sample analyses, complaints, drug quality reporting system (DQRS) reports, recalls, etc., and the compliance actions resulting from them or from past inspections. A Full Inspection may

revert to the Abbreviated Inspection Option, *with District concurrence,* based on findings of objectionable conditions as listed in Part V in one or more systems (a minimum of two systems must be completed).

c. Evaluate if important changes have occurred by comparing current operations against the EIR for the previous full inspection. The following types of changes are typical of those that warrant the Full Inspection Option:
   - New potential for cross-contamination arising through change in process or product line
   - Use of new technology requiring new expertise, significant new equipment, or new facilities

d. A Full Inspection may also be conducted on a surveillance basis at the District's discretion.

e. The Full Inspection Option will satisfy the biennial inspection requirement.

f. Follow-up to a Warning Letter or other significant regulatory actions should require a Full Inspection Option.

2. *Selecting the Abbreviated Inspection Option* — The Abbreviated Inspection Option normally will include inspection audit of at least two systems, one of which must be the Quality System. During the course of an abbreviated inspection, verification of quality system activities may require limited coverage in other systems.
   a. This option involves an inspection of the manufacturer to maintain surveillance over the firm's activities and to provide input to the firm on maintaining and improving the GMP level of assurance of quality of its products.
   b. A full inspection may revert to the Abbreviated Inspection Option, *with District concurrence,* based on findings of objectionable conditions as listed in Part V in one or more systems (a minimum of two systems must be completed).
   c. An abbreviated inspection is adequate for routine coverage and will satisfy the biennial inspectional requirement.

a. Comprehensive Inspection Coverage

It is not anticipated that full inspections will be conducted every 2 years. They may be conducted at less frequent intervals, perhaps at every third or fourth inspection cycle. Districts should consider selecting different optional systems for inspection coverage as a cycle of Abbreviated inspections are carried out to build comprehensive information on the firm's total manufacturing activities.

3. System Inspection Coverage

a. Quality System

Assessment of the Quality System is two-phased:

1. The first phase evaluates whether the Quality Control Unit has fulfilled the responsibility to review and approve all procedures related to production, quality control, and quality assurance and assure the procedures are adequate for their intended use. This also includes the associated record-keeping systems.
2. The second phase assesses the data collected to identify quality problems and may link to other major systems for inspectional coverage.

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other major systems that would warrant expansion of coverage. All areas under this system should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- *Product reviews* — at least annually; should include information from areas listed below as appropriate; batches reviewed for each product are representative of all batches manufactured; trends are identified (refer to 21 CFR 211.180(e))
- *Complaint reviews (quality and medical)* — documented; evaluated; investigated in a timely manner; includes corrective action where appropriate
- *Discrepancy and failure investigations related to manufacturing and testing* — documented; evaluated; investigated in a timely manner; includes corrective action where appropriate
- *Change control* — documented; evaluated; approved; need for revalidation assessed
- *Product improvement projects* — for marketed products
- *Reprocess/rework* — evaluation, review, and approval; impact on validation and stability
- *Returns/salvages* — assessment; investigation expanded where warranted; disposition
- *Rejects* — investigation expanded where warranted; corrective action where appropriate

- *Stability failures* — investigation expanded where warranted; need for field alerts evaluated; disposition
- Quarantine products
- *Validation* — status of required validation/revalidation (e.g., computer, manufacturing process, laboratory methods)
- Training/qualification of employees in quality control unit functions

b. Facilities and Equipment System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

1. Facilities

- Cleaning and maintenance
- Facility layout and air handling systems for prevention of cross-contamination (e.g., penicillin, beta-lactams, steroids, hormones, cytotoxics, etc.)
- Specifically designed areas for the manufacturing operations performed by the firm to prevent contamination or mix-ups
- General air handling systems
- Control system for implementing changes in the building
- Lighting, potable water, washing and toilet facilities, sewage and refuse disposal
- Sanitation of the building, use of rodenticides, fungicides, insecticides, and cleaning and sanitizing agents

2. Equipment

- Equipment installation and operational qualification where appropriate
- Adequacy of equipment design, size, and location
- Equipment surfaces should not be reactive, additive, or absorptive
- Appropriate use of equipment operations substances (lubricants, coolants, refrigerants, etc.), contacting products, containers, etc.
- Cleaning procedures and cleaning validation
- Controls to prevent contamination, particularly with any pesticides or any other toxic materials, or other drug or nondrug chemicals
- Qualification, calibration, and maintenance of storage equipment, such as refrigerators and freezers for ensuring that standards, raw materials, and reagents are stored at the proper temperatures
- Equipment qualification, calibration, and maintenance, including computer qualification/validation and security
- Control system for implementing changes in the equipment
- Equipment identification practices (where appropriate)
- Documented investigation into any unexpected discrepancy

c. Materials System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- Training/qualification of personnel
- Identification of components, containers, and closures
- Inventory of components, containers, and closures
- Storage conditions
- Storage under quarantine until tested or examined and released
- Representative samples collected, tested, or examined using appropriate means
- At least one specific identity test is conducted on each lot of each component
- A visual identification is conducted on each lot of containers and closures
- Testing or validation of supplier's test results for components, containers, and closures
- Rejection of any component, container, or closure not meeting acceptance requirements

Investigate fully the firm's procedures for verification of the source of components.

- Appropriate retesting/reexamination of components, containers, and closures
- First in–first out use of components, containers, and closures

- Quarantine of rejected materials
- Water and process gas supply, design, maintenance, validation, and operation
- Containers and closures should not be additive, reactive, or absorptive to the drug product
- Control system for implementing changes in the materials handling operations
- Qualification/validation and security of computerized or automated processes
- Finished product distribution records by lot
- Documented investigation into any unexpected discrepancy

d. Production System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- Training/qualification of personnel
- Control system for implementing changes in processes
- Adequate procedure and practice for charge-in of components
- Formulation/manufacturing at not less than 100%
- Identification of equipment with contents, and, where appropriate, phase of manufacturing or status
- Validation and verification of cleaning/sterilization/depyrogenation of containers and closures
- Calculation and documentation of actual yields and percentage of theoretical yields
- Contemporaneous and complete batch production documentation
- Establishing time limits for completion of phases of production
- Implementation and documentation of in-process controls, tests, and examinations (e.g., pH, adequacy of mix, weight variation, clarity)
- Justification and consistency of in-process specifications and drug product final specifications
- Prevention of objectionable microorganisms in unsterile drug products
- Adherence to preprocessing procedures (e.g., setup, line clearance, etc.)
- Equipment cleaning and use logs
- Master production and control records
- Batch production and control records
- Process validation, including validation and security of computerized or automated processes
- Change control; the need for revalidation evaluated
- Documented investigation into any unexpected discrepancy

e. Packaging and Labeling System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited only to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- Training/qualification of personnel
- Acceptance operations for packaging and labeling materials
- Control system for implementing changes in packaging and labeling operations
- Adequate storage for labels and labeling, both approved and returned after issued
- Control of labels that are similar in size, shape, and color for different products
- Finished product cut labels for immediate containers that are similar in appearance without some type of 100% electronic or visual verification system or the use of dedicated lines
- Labels are not gang printed unless they are differentiated by size, shape, or color
- Control of filled unlabeled containers that are later labeled under multiple private labels
- Adequate packaging records that will include specimens of all labels used
- Control of issuance of labeling, examination of issued labels, and reconciliation of used labels
- Examination of the labeled finished product
- Adequate inspection (proofing) of incoming labeling
- Use of lot numbers and the destruction of excess labeling bearing lot/control numbers
- Physical/spatial separation between different labeling and packaging lines
- Monitoring of printing devices associated with manufacturing lines

- Line clearance, inspection, and documentation
- Adequate expiration dates on the label
- Conformance to tamper-evident packaging (TEP) requirements (see 21CFR 211.132 and Compliance Policy Guide, 7132a.17)
- Validation of packaging and labeling operations, including validation and security of computerized processes
- Documented investigation into any unexpected discrepancy

f. Laboratory Control System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited only to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- Training/qualification of personnel
- Adequacy of staffing for laboratory operations
- Adequacy of equipment and facility for intended use
- Calibration and maintenance programs for analytical instruments and equipment
- Validation and security of computerized or automated processes
- Reference standards: source, purity and assay, and tests to establish equivalency to current official reference standards as appropriate
- System suitability checks on chromatographic systems [e.g., gas chromatography (GC) or high pressure liquid chromatography (HPLC)]
- Specifications, standards, and representative sampling plans
- Adherence to the written methods of analysis
- Validation/verification of analytical methods
- Control system for implementing changes in laboratory operations
- Required testing is performed on the correct samples
- Documented investigation into any unexpected discrepancy
- Complete analytical records from all tests and summaries of results
- Quality and retention of raw data (e.g., chromatograms and spectra)
- Correlation of result summaries to raw data; presence of unused data
- Adherence to an adequate Out of Specification (OOS) procedure that includes timely completion of the investigation
- Adequate reserve samples; documentation of reserve sample examination
- Stability testing program, including demonstration of stability indicating capability of the test methods

4. Sampling

Samples of defective product constitute persuasive evidence that significant CGMP problems exist. Physical samples may be an integral part of a CGMP inspection where control deficiencies are observed. Physical samples should be correlated with observed control deficiencies. Consider consulting your servicing laboratory for guidance on quantity and type of samples (in-process or finished) to be collected. Documentary samples may be submitted when the documentation illustrates the deficiencies better than a physical sample. Districts may elect to collect, but not analyze, physical samples or to collect documentary samples to document CGMP deficiencies. Physical sample analysis is not necessary to document CGMP deficiencies.

When a large number of products have been produced under deficient controls, collect physical or documentary samples of products that have the greatest therapeutic significance, narrow range of toxicity, or low dosage strength. Include samples of products of minimal therapeutic significance only when they illustrate highly significant CGMP deficiencies.

5. Inspection Teams

An inspection team (see IOM 502.4) composed of experts from within the District, other Districts, or Headquarters is encouraged when it provides needed expertise and experience. Contact the ORO/Division of Field Investigations if technical assistance is needed (see also FMD 142). Participation of an analyst (chemist or microbiologist) on an inspection team is also encouraged, especially where laboratory issues are extensive or complex. Contact your Drug Servicing Laboratory or ORO/Division of Field Science.

6. Reporting

The investigator utilizes Subchapter 590 of the IOM for guidance in reporting of inspectional findings. The Summary of Findings should identify systems covered. The body of the report should identify and explain the rationale for inspecting the profile classes covered. Any adverse findings by systems under separate captions should be reported and discussed in full. Additional information should be provided as needed or desired, for example, a

description of any significant changes that have occurred since previous inspections.

Reports with specific, specialized information required should be prepared as instructed within the individual assignment/attachment.

V. ANALYTICAL OBSERVATIONS

A. Analyzing Laboratories

1. Routine chemical analyses — all Servicing Laboratories except WEAC.
2. Sterility testing:
   Region Examining Laboratory
3. Other microbiological examinations — NRL (for the CE Region), SRL, SAN, and DEN; Salmonella Serotyping Lab — ARL.
4. Chemical cross-contamination analyses by mass spectrometry (MS) — NRL, SRL, DEN, PRL/NW, and PHI. Non-mass-spectrometry laboratories should call one of their own regional MS-capable laboratories or Division of Field Science (HFC-140) to determine the most appropriate lab for the determinations to be performed.
5. Chemical cross-contamination analyses by nuclear magnetic resonance (NMR) spectroscopy — NRL. Non-NMR laboratories should call one of their own regional labs equipped with NMR or Division of Field Science (HFC-140) to determine the most appropriate lab for the determinations to be performed.
6. Dissolution testing — NRL, KAN, SRL, SJN, DET, PHI, DEN, PRL/SW, and PRL-NW. Districts without dissolution testing capability should use one of their own regional labs for dissolution testing. Otherwise, call DFS.
7. Antibiotic analyses:
   ORA Examining Laboratory
   Denver District Lab (HFR-SW260)
   Tetracyclines
   Erythromycins
   Northeast Regional Lab (HFR-NE500)
   Penicillins
   Cephalosporins
   CDER Examining Laboratory
   Office of Testing and Research
   Division of Pharmaceutical Analysis (HFD-473)
   All other antibiotics
8. Bioassays — Division of Testing and Applied Analytical Research, Drug Bioanalysis Branch (HFN-471).
9. Particulate Matter in Injectables — NRL, SRL.
10. Pyrogen/LAL Testing — SRL.

B. Analysis

1. Samples must be examined for compliance with applicable specifications as they relate to deficiencies noted during the inspection. The official method should be used for check analyses or, when no official method exists, by other validated procedures.
2. The presence of cross-contamination must be confirmed by a second method. Spectroscopic methods, such as MS, NMR, ultraviolet (UV)-Visible, or infrared (IR) are preferred. A second confirmatory method should be employed by different mechanisms than the initial analysis (i.e., ion-pairing vs. conventional reverse phase HPLC).
3. Check Analysis for dissolution rate must be performed by a second dissolution-testing laboratory.
4. Sterility testing methods should be based on current editions of USP and the *Sterility Analytical Manual*. Other microbiological examinations should be based on appropriate sections of USP and BAM.

VI. REGULATORY/ADMINISTRATIVE STRATEGY

Inspection findings that demonstrate that a firm is not operating in a state of control may be used as evidence for taking appropriate advisory, administrative, or judicial actions.

When the management of the firm is unwilling or unable to provide adequate corrective actions in an appropriate time frame, formal agency regulatory actions will be recommended that are designed to meet the situation encountered.

When deciding the type of action to recommend, the initial decision should be based on the seriousness of the problem and the most effective way to protect consumers. Outstanding instructions in the *Regulatory Procedures Manual* (*RPM*) should be followed.

The endorsement to the inspection report should point out the actions that have been taken or will be taken and when. All deficiencies noted in inspections/audits under this program must be addressed by stating the firm's corrective actions, accomplished or projected, for each as established in the discussion with management at the close of the inspection.

All corrective action approaches in domestic firms are monitored and managed by the District Offices. The approaches may range from shutdown of operations, recall of products, conducting testing programs, development of new procedures, modifications of plants and equipment,

to simple immediate corrections of conditions. CDER/DMPQ/CMGB/HFD-325 will assist District Offices as requested.

An inspection report that documents that one or more systems is/are out of control should be classified as OAI. District Offices may issue Warning Letters per RPM to warn firms of violations, to solicit voluntary corrections, and to provide for the initial phase of formal agency regulatory actions.

Issuance of a Warning Letter or taking other regulatory actions pursuant to a surveillance inspection (other than a For Cause Inspection) should result in the classification of all profile classes as unacceptable. Also, the inspection findings will be used as the basis for updating profile classes in FACTS.

The FDA laboratory tests that demonstrate the effects of absent or inadequate CGMPs are strong evidence for supporting regulatory actions. Such evidence development should be considered as an inspection progresses and deficiencies are found; however, the lack of violative physical samples is *not* a barrier to pursuing regulatory or administrative action, provided that CGMP deficiencies have been well documented. Likewise, physical samples found to be in compliance are *not* a barrier to pursuing action under CGMP charges.

Evidence to support significant deficiencies or a trend of deficiencies within a system covered could demonstrate the failure of a system and should result in consideration of the issuance of a Warning Letter or other regulatory action by the District. When deciding the type of action to recommend, the initial decision should be based on the seriousness or the frequency of the problem. Examples include the following:

Quality System

1. Pattern of failure to review/approve procedures
2. Pattern of failure to document execution of operations as required
3. Pattern of failure to review documentation
4. Pattern of failure to conduct investigations and resolve discrepancies/failures/deviations/complaints
5. Pattern of failure to assess other systems to assure compliance with GMP and SOPs

Facilities and Equipment

1. Contamination with filth, objectionable microorganisms, toxic chemicals or other drug chemicals, or a reasonable potential for contamination, with demonstrated avenues of contamination, such as airborne or through unclean equipment
2. Pattern of failure to validate cleaning procedures for non-dedicated equipment; lack of demonstration of effectiveness of cleaning for dedicated equipment
3. Pattern of failure to document investigation of discrepancies
4. Pattern of failure to establish/follow a control system for implementing changes in the equipment
5. Pattern of failure to qualify equipment, including computers

Materials System

1. Release of materials for use or distribution that do not conform to established specifications
2. Pattern of failure to conduct one specific identity test for components
3. Pattern of failure to document investigation of discrepancies
4. Pattern of failure to establish/follow a control system for implementing changes in the materials handling operations
5. Lack of validation of water systems as required depending upon the intended use of the water
6. Lack of validation of computerized processes

Production System

1. Pattern of failure to establish/follow a control system for implementing changes in the production system operations
2. Pattern of failure to document investigation of discrepancies
3. Lack of process validation
4. Lack of validation of computerized processes
5. Pattern of incomplete or missing batch production records
6. Pattern of nonconformance to established in-process controls, tests, and specifications

Packaging and Labeling

1. Pattern of failure to establish/follow a control system for implementing changes in the packaging or labeling operations
2. Pattern of failure to document investigation of discrepancies
3. Lack of validation of computerized processes
4. Lack of control of packaging and labeling operations that may introduce a potential for mislabeling
5. Lack of packaging validation

Laboratory Control System

1. Pattern of failure to establish/follow a control system for implementing changes in the laboratory operations
2. Pattern of failure to document investigation of discrepancies
3. Lack of validation of computerized and/or automated processes
4. Pattern of inadequate sampling practices
5. Lack of validated analytical methods
6. Pattern of failure to follow approved analytical procedures
7. Pattern of failure to follow an adequate OOS procedure
8. Pattern of failure to retain raw data
9. Lack of stability indicating methods
10. Pattern of failure to follow stability programs

Follow-up to a Warning Letter or other significant regulatory action because of an abbreviated inspection should warrant full inspection coverage as defined in this program.